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ORIGINAL ARTICLE

Safety and efficacy of botulinum toxin type A following long-term use

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Botulinum toxin serotype A (BoNT-A) has long heritage of use leading to confidence in its safety and efficacy. The application of BoNT-A does not lead to persistent histological changes in the nerve terminal or the target muscle. Clinical trials defined the safety and tolerability profile of BoNT-A across common therapeutic indications and showed an incidence of adverse events of approximately 25% in the BoNT-A-treated group compared with 15% in the control group. Focal weakness was the only adverse event to occur more often following BoNT-A treatment. Long-term BoNT-A administration has been assessed in various treatment settings, with the level and duration of BoNT-A efficacy response being maintained over repeated rounds of injection with no major safety concerns. The treatment of children with cerebral palsy often require long-term, repeated, multimuscle BoNT-A injections that lead to the administration of comparably higher toxin doses. Despite the high total body doses used, their distribution over multiple muscles and injection sites means that systemic side effects are rare. Recent formulation changes have reduced the incidence of antibody development following treatment with BOTOX®. These findings show long-term BoNT-A treatment to be both safe and efficacious for a wide variety of indications.

Introduction

Botulinum toxin serotype A (BoNT-A) has long heritage of use in the area of neurological treatment, which has led to the high level of confidence in its long-term safety and efficacy and its application to new indications. Key factors associated with building confidence in any new therapeutic agent are good and reproducible efficacy and safety results demonstrated in well-controlled clinical trials; the development of a substantial body of supportive background literature and subsequently the demonstration of continued efficacy in the long term. Specific factors, pertinent to building confidence in the long-term therapeutic use of BoNT-A have become apparent with increased use of the different commercially available formulations. These factors are primarily associated with whether there is evidence of migration of the toxin from the target muscle leading to systemic side effects and whether long-term use is associated with the development of neutralizing antibodies against BoNT-A.

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A wealth of evidence, indicative of the long-term safety and efficacy of BoNT-A, has accumulated as a result of many years of toxin use in a variety of clinical indications. For example, BoNT-A has been used for the treatment of abnormal muscle contractions in the extrinsic eye muscles (blepharospasm) since 1980, in cervical muscles since 1985, in laryngeal muscles since 1986, in oromandibular and limb muscles since 1989 and in the bladder detrusor since 1990. As a result, BoNT-A has a long heritage, in excess of 15 years, of clinical usage that has proved its value as a therapeutic treatment. The extensive evidence base relating to the use of this toxin is highlighted by the findings of a Medline search performed in August 2004, which yielded over 1800 scientific and medical citations for BoNT-A.

The safety profile of botulinum toxin serotype A

The Food and Drug Administration defines an adverse event as any untoward medical occurrence that may be local or systemic [1]. Local reactions to BoNT-A at the administration site commonly include pain, oedema, erythema, ecchymosis, headache and short-term hyperaesthesia. In addition, local reactions can occur following migration of the toxin into adjacent muscles

[2]. For example, in cervical dystonia, BoNT-A administration into the sternocleidomastoid muscle can lead to the occurrence of dysphagia following toxin migration into the nearby pharyngeal muscles [3,4]. BoNT-A treatment of blepharospasm or hemifacial spasm can lead to ptosis following local diffusion of the toxin; however, optimal targeting of the pre-tarsal rather than the orbital portion of the orbicularis oculi muscle reduces the incidence of this adverse event [5]. Therefore, clinical experience, leading to optimal muscle targeting, is an important factor in minimizing BoNT-A migration and improving the safety profile of this treatment. In addition, the various BoNT-A formulations have differing migration patterns from the target muscle, which should be taken into account.

Systemic adverse reactions following BoNT-A administration primarily comprise nausea, fatigue, malaise, flu-like symptoms and rash. Specific systemic adverse events may be associated with toxin migration into particular muscles, for example, treatment of cervical dystonia is often associated with dry mouth, possibly as a result of systemic distribution of the toxin. There is limited evidence of distant neuromuscular effects, as a result of single-fibre electromyographic studies; however, the clinical significance of these observations is likely to be negligible [6].

Histological evidence of botulinum toxin safety

Two histological studies have shown that the neuronal and muscular changes that occur following BoNT-A administration are fully reversible, indicating the safety of the treatment. Borodic and Ferrante [7] evaluated the histological changes that occurred in the orbicularis oculi muscles of 11 patients with essential blepharospasm or Meige's syndrome. Samples were taken from patients who had experienced treatment failure with BoNT-A after receiving an average of 11.3 injections over 3.5 years. In muscle samples taken 7 weeks after treatment, there was considerable variability in the structure of the muscle fibres, with some appearing shrunken. However, in muscle samples taken 12 weeks after BoNT-A injection, the fibre diameter had returned to normal and acetylcholinesterase staining was limited to the neuromuscular junctions. Therefore, this study provides evidence that repeated BoNT-A injections into human muscle do not cause irreversible muscle atrophy or other degenerative changes.

In the second study [8], an animal model was used to visualize nerve terminals in the mouse sternomastoid muscle following BoNT-A treatment. The study showed that blockade of the motor end plate by BoNT-A resulted in the formation of numerous nerve sprouts from the parent nerve. These nerve sprouts extended into the muscle and were capable of eliciting muscle contraction. However, long-term analysis of the physiology of BoNT-A treated nerves showed that approximately 3 months after treatment the motor end plates regained the ability to release acetylcholine and that this was associated with regression of the nerve sprouts.

Long-term safety and efficacy of botulinum toxin treatment

Safety assessments for specific BoNT-A indications have been published as *Cochrane Systematic Reviews* and incorporated into European guidelines [9]. These assessments primarily consider data from randomized clinical trials in which BoNT-A injection is compared with placebo treatment. The majority of the information comes from trials using BOTOX® (Allergan Inc., Irvine, California, USA), with the information on Dysport® (Ipsen Limited, Berkshire, UK) being more limited.

Assessments of BoNT-A use in hemifacial spasm and blepharospasm identified a paucity of randomized clinical trial data using both BoNT-A formulations. Despite this, the overall findings were that BoNT-A administration resulted in such a substantial therapeutic benefit that treatment was recommended as safe and effective for both indications [10,11]. A more substantial body of randomized clinical trial evidence was identified for assessment of the efficacy of BoNT-A in treating cervical dystonia [12]. This meta-analysis reported that only adverse events associated with the mechanism of action of BoNT-A were more frequent in the active treatment group, resulting in side-effects such as neck weakness, dysphagia, dry mouth, sore throat, voice changes and hoarseness. A clear dose–response relationship was demonstrated for the frequency and severity of adverse events.

As clinical use has shown that different BoNT-A formulations exhibit subtle differences in both efficacy and safety characteristics, it is considered appropriate to assess data using a product-specific approach [13]. The safety of BOTOX administration was assessed using meta-analysis of data from 36 randomized clinical trials [13]. This analysis has recently been repeated to include safety data from 37 randomized, controlled trials comparing BOTOX to placebo or an active comparator, for indications including dystonia and movement disorders (10 studies), spasticity and cerebral palsy (9 studies), gastrointestinal and urological conditions (7 studies), pain and headache (5 studies), hyperhidrosis (3 studies) and cosmetic use (3 studies) (Naumann, unpublished data). The meta-analysis considered data from 2361 subjects, of whom 1447 received BOTOX and 914 received control treatment. Figure 1

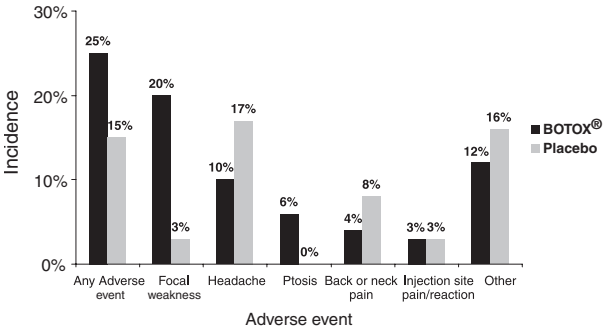

Figure 1 Meta-analysis assessing incidence of adverse events following BoNT-A and placebo treatment.

shows the overall incidence of adverse events and the incidence of specific events in the two study populations. The incidence of adverse events showed a rate of approximately 25% in BOTOX-treated subjects (365 of 1447) compared with 15% in the control group (136 of 914). When considering specific adverse events, only focal muscle weakness and ptosis occurred at a higher incidence following BOTOX treatment when compared with the control group. All adverse events were mild to moderate in severity, and none of the studies assessed reported any severe events. These results demonstrate the favourable safety profile of BOTOX across a broad spectrum of therapeutic indications, and as the primary adverse events are focal conditions, it suggests that this formulation does not migrate from the injection site.

As BoNT-A therapy began in the 1980s and efficacy usually persists in excess of 4 months, a sizeable group of patients have received repeated injections for the long-term management of their condition. Mejia *et al.* [14] assessed the long-term efficacy and safety of BoNT-A treatment in a group of 45 patients who had received repeated injections at the Baylor College of Medicine over at least 12 years. All patients received regular BoNT-A treatments over a mean 15.8 ± 1.5 years, for indications such as cervical, cranial, focal or oromandibular dystonia, blepharospasm, dysphonia, hemidystonia and hemifacial spasm. The changes in efficacy data comparing the first and last treatments are summarized in Fig. 2. The overall BoNT-A dose administered increased from 154.3 ± 98.9 U at the first injection to 221.1 ± 129.4 U at the last injection ($P < 0.0001$). The duration of maximal response increased from 9.3 ± 6.4 weeks following the first injection to 13.9 ± 0.5 weeks at the last injection ($P < 0.005$). Both the global efficacy rating ($P < 0.02$) and the peak effect score ($P < 0.05$) improved when comparing the first and last treatment sessions.

A total of 20 adverse events occurred in 35.6% of patients (16 of 45) following their initial treatment visit, with common adverse events of ptosis and dysphagia being reported and isolated occurrences of neck and generalized weakness, malaise and gastrointestinal problems. This analysis showed that BoNT-A retained efficacy and was not associated with major safety concerns when administered for periods of up to 18 years.

A recent study considered long-term BoNT-A treatment of 275 patients at the University of Zagreb, of whom 70% had in excess of 12 years continuous therapy for various movement disorders [15]. The study showed that 34% of patients experienced adverse events after their first treatment visit but that the overall incidence did not increase with long-term therapy. The dose administered per visit and the peak duration of response did not change when comparing different treatment periods. However, the peak clinical effect improved over the course of treatment ($P < 0.05$).

The long-term efficacy and safety of BoNT-A treatment have been considered for a number of specific clinical indications. Hsiung *et al.* [16] conducted a retrospective analysis of 235 patients treated with BOTOX for movement disorders, including cervical dystonia, hemifacial spasm and blepharospasm, over a 10-year period. Treatment benefit was sustained in 76% of

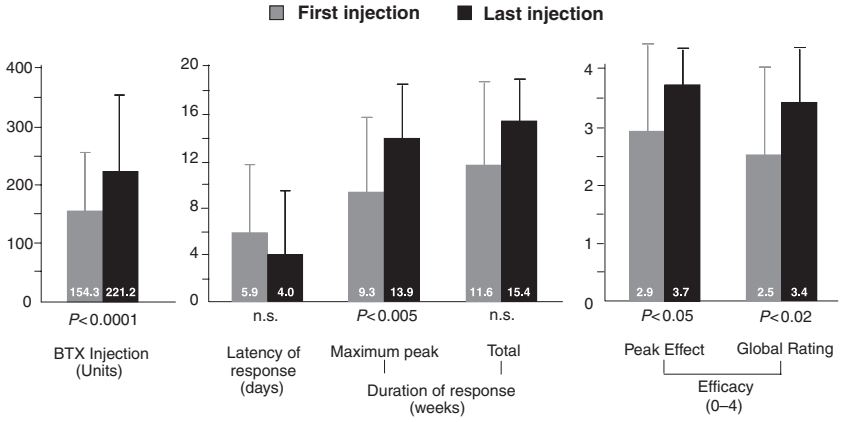

Figure 2 The effect of long-term botulinum toxin serotype A treatment on efficacy parameters.

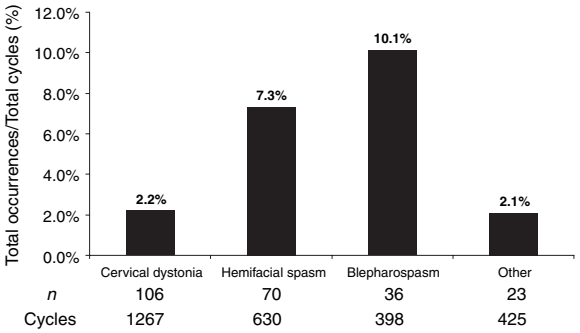

Figure 3 Incidence of adverse events during long-term therapy, according to clinical indication.

patients at the 5-year assessment. Adverse events were reported by 27% of patients, at 4.5% of the 2616 treatments, and comprised primarily dysphagia, ptosis and dry eyes. The profile of adverse events according to clinical indication is summarized in Fig. 3, and shows that the highest incidence of adverse events per treatment cycle occurred in patients with blepharospasm. In another study, 27 patients received BOTOX injection to treat essential blepharospasm and idiopathic hemifacial spasm over a 4- to 6-year period [17]. No systemic adverse events were reported following administration of a total of 443 injections, but all patients experienced minor and transient side effects, commonly of dry eye and ptosis. No patients experienced orbicularis muscle atrophy. In other studies, the treatment of cervical dystonia [18], oromandibular dystonia [19] or hemifacial spasm [20] over periods of approximately 10 years showed incidences of adverse events ranging from 31% to 37%, most of which were localized and transient. Defazio *et al.* [20] showed that sustained symptom relief was associated with a reduction in the incidence of adverse events when comparing the 1st and 10th years of treatment (36.9% in year 1 falling to 12.3% in year 10, $P < 0.05$).

The long-term safety and efficacy of BoNT-A treatment are also well documented for the treatment of cerebral palsy. In these patients, spasticity and dystonia are combined in multiple muscles, contributing to the overall disease characteristics. Furthermore, the clinical picture changes as the child grows and undergoes motor development. Current standards of BoNT-A treatment usually involve the treatment of multiple muscles in each session and require the administration of high cumulative doses of BoNT-A, often up to 25 U BOTOX/kg body weight [21,22]. Recent analysis of a comprehensive database with long-term follow-up has shown that the correct use of high doses during multimuscle treatment is rarely associated with systemic side effects, as the total dose is distributed over multiple muscles and over multiple injection sites per muscle [23]. The incidence of side effects associated with multimuscle BoNT-A administration is recognized to be less than 10% and the events are usually mild and transient in nature. However, it should be noted that the body of experience concerning multimuscle treatment relates to the use of the BOTOX formulation, with very little data being available on multimuscle treatment in children using Dysport.

Botulinum toxin immunogenicity

The major factor that can impact on the long-term efficacy of BoNT-A is the development of neutralizing antibodies, which can induce secondary non-responsiveness [24,25]. A number of risk factors promote anti-BoNT antibody formation, such as a short interval between injections, the administration of booster injections if optimal efficacy is not achieved, the use of increasing BoNT doses at each injection, a high cumulative BoNT dose and early onset of BoNT therapy. In addition, unclassified patient characteristics may predispose certain individuals to produce neutralizing antibodies. However, it should be noted that the production of low-titre antibodies may not interfere with BoNT's clinical effects [26]. It is likely that only high antibody titres will result in partial or complete failure of therapy.

The overall rate of antibody formation following administration of Dysport is comparable with that initially seen with BOTOX, with an incidence of approximately 5% [24]. In early studies, neutralizing antibodies were estimated to develop in 32% of cerebral palsy patients receiving BoNT-A [25] and in 2% of cervical dystonia patients treated with BOTOX [27]. However, the introduction in 1997 of a new BOTOX formulation, having an 80% reduction in total protein content, reduced the incidence of neutralizing antibody formation to approximately 1% [24]. In patients with hemifacial spasm, the old BOTOX formulation resulted in neutralizing anti-BoNT-A antibodies being produced by 9.5% of patients, compared with 0% using the new preparation [28]. Other studies have shown incidences of antibody formation using the new BOTOX formulation of 0.1% for axillary hyperhidrosis patients [29] and 0.4% for cervical dystonia patients [30]. Recent evidence considers the development of antibodies against the new BOTOX formulation to occur with an incidence of less than 1% across the range of licensed indications [31].

The potential impact of neutralizing antibody formation on efficacy was considered by Brashear *et al.* [32], who assessed whether long-term treatment required progressive dose escalation to maintain responsiveness. The retrospective review of 172 cervical dystonia patients

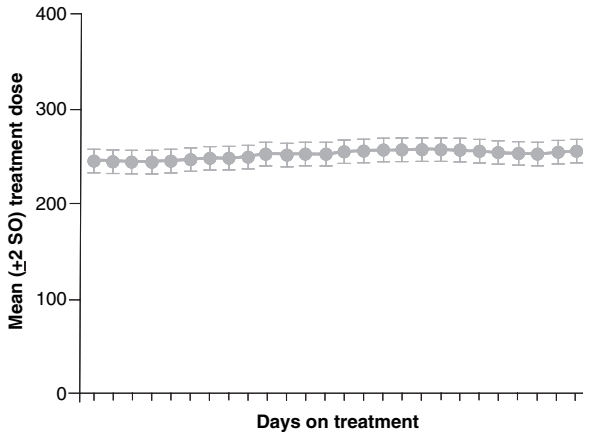

Figure 4 The mean dose of BOTOX® administered over a 2-year study period in cervical dystonia patients.

treated with BOTOX assessed the mean dose administered over a 2-year period. The data are summarized in Fig. 4 and show that there was no clinically relevant impairment of efficacy over the 2-year treatment period as evidenced by the consistency of dose administered. In addition, the intervals between BOTOX administration remained constant, suggesting no decline in the duration of effect despite long-term treatment.

Conclusions

The BoNT-A is extremely effective across a broad spectrum of clinical indications and has an excellent safety and tolerability profile. The safety and efficacy findings accumulated during long-term clinical use over the last 10 years are supported by pre-clinical studies and the evidence from randomized clinical trials. The excellent safety profile of BoNT-A is related to its focal and non-systemic mode of administration and allows the use of high total body doses to be administered in a multimuscle setting. The development of new BoNT-A formulations, such as BOTOX, has reduced the risk of neutralizing antibody formation, which might compromise efficacy responses. On the basis of the evidence of efficacy and safety, it is anticipated that understanding of the specifics of the different preparations will allow upgrading and fine-tuning of future treatment.

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Declaration of interest

Prof. Markus Naumann has received honorarium payments from Allergan for his work on botulinum toxin therapy. Prof. Alberto Albanese has received honorarium payments from Allergan and educational grants from Ipsen for his work on botulinum toxin therapy. Prof. Florian Heinen has received honorarium payments for lectures and educational grants from Allergan, Ipsen and Merz for his work on botulinum toxin therapy. Prof. Guy Molenaers has received an unrestricted educational grant from Allergan for previous research projects on botulinum toxin therapy in children with cerebral palsy. Prof. Maja Relja has received education grants from Allergan for her work on botulinum toxin type A therapy.

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